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Portal vein thrombosis, cirrhosis, and liver transplantation

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Summary

Portal vein thrombosis is not uncommon in candidates for transplantation. Partial thrombosis is more common than complete thrombosis. Despite careful screening at evaluation, a number of patients are still found with previously unrecognized thrombosis per-operatively. The objective is to recanalize the portal vein or, if recanalization is not achievable, to prevent the extension of the thrombus so that a splanchnic vein can be used as the inflow vessel to restore physiological blood flow to the allograft. Anticoagulation during waiting time and transjugular intrahepatic portosystemic shunt (TIPS) are two options to achieve these goals. TIPS may achieve recanalization in patients with complete portal vein thrombosis. However, a marked impairment in liver function, which is a characteristic feature of most candidates for transplantation, may be a contraindication for TIPS. Importantly, the MELD score is artificially increased by the administration of vitamin K antagonists due to prolonged INR. When patency of the portal vein and/or superior mesenteric vein is not achieved, only non-anatomical techniques (renoportal anastomosis or cavoportal hemitransposition) can be performed. These techniques, which do not fully reverse portal hypertension, are associated with higher morbidity and mortality risks. Multivisceral transplantation including the liver and small bowel needs to be evaluated. In the absence of prothrombotic states that may persist after transplantation, there is no evidence that pre-transplant portal vein thrombosis justifies long term anticoagulation post-transplantation, provided portal flow has been restored through conventional end-to-end portal anastomosis.

Keywords: Portal vein thrombosis; Liver transplantation; Portal hypertension; Anticoagulation; Vitamin K antagonists.

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Abbreviations: PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; VKA, vitamin K antagonists; LMWH, low molecular weight heparin; TIPS, transjugular intrahepatic portosystemic shunt.

Introduction

Restoring both portal and arterial blood flow to the allograft is a necessary condition for liver transplantation to be successful. While arterial blood flow is the only source of oxygen supply to the donor's biliary tract, portal blood flow ensures most of the oxygen supply to the parenchyma, which is crucial for recovery of liver function. In addition, restoration of the portal flow through the allograft rapidly reverses portal hypertension, which is a major source of complications in cirrhosis.

Portal vein thrombosis (PVT) is increasingly recognized in cirrhotic patients, especially in candidates for transplantation. Indeed, these patients have detailed imaging at evaluation and thereafter, repeated imaging, which offers the opportunity to recognize thrombosis occurring while on the waiting list. PVT is most often asymptomatic in patients with advanced cirrhosis so that diagnosis is based on systematic imaging. The proper impact of PVT on the natural history of cirrhosis remains unclear [1]. There is no evidence that PVT leads to further deterioration in liver function in advanced cirrhosis. However, independent of clinical course and disease severity, PVT may be a source of technical difficulties in the particular setting of transplantation, with a negative impact on the outcome. Occasionally, it may represent a definitive contraindication for transplantation. This review examines issues concerning the incidence, predisposing factors, and management of PVT in candidates for liver transplantation. We also discuss issues concerning the impact of PVT on the outcome and surgical alternatives in patients with extensive thrombosis.

Incidence, mechanisms, and consequences of portal vein thrombosis in cirrhosis

The prevalence of PVT in cirrhotic patients at evaluation or at the time of transplantation varies from 5% to 26% (Table 1) [2–11]. The majority of patients have partial thrombosis. The relatively high prevalence of PVT in candidates for transplantation could be related to more advanced disease. However, the prevalence of PVT in candidates for transplantation seems to be similar to that found in cirrhotic patients who were not necessarily evaluated for transplantation [3,12,13]. Even in the most recent series, a significant proportion of patients with PVT at the time of surgery were previously unrecognized (up to 50%) [4,9]. This finding could be related to either false negatives on imaging at evaluation or to thrombosis occurring while on the waiting list. The rate of false negatives may obviously vary according to

Table 1. Prevalence of portal vein thrombosis in patients undergoing evaluation for transplantation or transplantation.

Author, [Ref.]	Year	Patients	Prevalence of PVT* (%)	Partial/complete PVT (%)	Timing of diagnosis of PVT
Gayowski *et al.*, [11]	1996	88	26	-	Transplantation
Yerdel *et al.*, [10]	2000	779	8	-	Transplantation
Manzanet *et al.*, [5]	2001	391	16	12/4	Transplantation
Molmenti *et al.*, [6]	2002	1546	5	-	Transplantation
Llado *et al.*, [2]	2005	355	12	-	Transplantation
Francoz *et al.*, [4]	2005	251	8	7/1	Evaluation†
Tao *et al.*, [7]	2009	465	9	-	Transplantation
Dumortier *et al.*, [9]	2010	468	8	7/1	Transplantation
Englesbe *et al.*, [3]	2010	574	5	0/5**	Transplantation
Ravaioli *et al.*, [8]	2011	889	10	6/4	Transplantation

*PVT, portal vein thrombosis.
**Patients with partial thrombosis were not considered.
†In this series, the incidence of *de novo* thrombosis from evaluation to transplantation was 7.4% for an average waiting time of 12 months.

different imaging protocols. However, even in patients undergoing
systematic ultrasound during waiting time at close intervals (every 3–4 months for instance), the rate of previously unrecognized thrombosis remains relatively high [9], emphasizing the need to improve screening. Few data have been reported on the incidence of thrombosis occurring while on the waiting list. In one study, the incidence was found to be of 7% for a mean waiting time of 12 months [4].

In non-cirrhotic patients, PVT is most often related to prothrombotic states (myeloproliferative neoplasms and/or inherited coagulation disorders) [14]. By contrast, in cirrhotic patients, portal hemodynamics seems to be the main factor leading to thrombosis. The characteristic parenchymal changes of cirrhosis as well as changes in vasoreactivity result in increased intrahepatic vascular resistance and reduced portal flow [15,16]. Paradoxically, low platelet count seems to be an independent predisposing factor for PVT in cirrhosis [4,16]. The inverse correlation between platelet count and PVT may be due to the fact that reduced portal flow resulting from portal hypertension outweighs a possibly "protective" effect of low platelet count against thrombosis [17]. Advanced cirrhosis is also characterized by a decrease in coagulation factors, which is theoretically viewed as "protective" against thrombosis. However, evidence shows that low coagulation factors do not exclude the occurrence of splanchnic and systemic thrombosis. Indeed, both pro and anticoagulant factors are decreased in cirrhosis, resulting in a compensated hemostatic balance [18,19]. Patients with cirrhotic and non-cirrhotic liver diseases, for instance, may be at higher risk of venous thromboembolism compared to controls [20]. Molecular studies have shown that some thrombophilic genotypes, including factor V Leiden mutation, may be more frequent in cirrhotic patients with PVT compared to cirrhotic patients without thrombosis [12,13]. The role of methylene tetrahydrofolate reductase mutation has not been clearly demonstrated. However, even in patients with compensated cirrhosis, it remains difficult to detect an underlying prothrombotic condition due to the non-specific decrease in coagulation factors and inhibitors [14]. The potential role of chronic inflammatory state resulting from bacterial products translocation in the pathogenesis of PVT needs to be further investigated.

Tumor invasion involving the branches and/or the trunk of the portal vein is a possible source of portal vein obstruction in patients with hepatocellular carcinoma (HCC). While, cruoric thrombosis may not preclude transplantation in patients with HCC [21], macroscopic vascular invasion by the tumor is a definitive contraindication. Therefore, in candidates for transplantation with HCC and portal vein obstruction, a clear distinction between tumor invasion and thrombosis should be made. High alpha fetoprotein level, endovascular obstruction adjacent to the tumor, enlargement of the vessel by the endovascular material and enhancement of the intravascular material at the arterial phase on imaging are consistent with tumor invasion [22]. Contrast-enhanced ultrasonography (US) may also help distinguish malignant invasion from cruoric thrombosis by showing an arterial signal within the endoluminal material [23].

The impact of PVT on the outcome of cirrhosis is an unresolved issue. As discussed above, PVT generally occurs in patients with advanced cirrhosis and severe portal hypertension. As a result, the issue of whether PVT is a mere marker of advanced disease or an event actually contributing to further deterioration in liver function has not been clearly addressed. Evidence that PVT is an independent prognostic factor in cirrhosis is still lacking.

Management of portal vein thrombosis in candidates for transplantation

The main objective in the management of PVT in candidates for transplantation is to achieve at least partial recanalization so that portal flow to the graft can be restored through conventional end-to-end portal vein anastomosis. When recanalization is not achievable, the objective is to prevent further extension of the thrombus during waiting time, especially to the superior mesenteric vein. Indeed, when neither the portal vein nor the superior mesenteric vein can be used, alternative (non-anatomical) techniques to restore portal flow are associated with increased morbidity and mortality. Careful screening for PVT at evaluation is crucial to achieve these goals. Repeated imaging during waiting time is also needed in order to detect thrombosis (Fig. 1A and B) [4].

Both Doppler ultrasonography (US) and multiphasic (arterial and portal) helical computed tomography (CT) can be recommended at evaluation. Doppler US is highly accurate at detecting thrombosis involving the trunk of the portal vein and in intrahepatic branches. It provides additional information concerning portal flow and its direction. CT helps better assess the superior mesenteric vein, spontaneous portosystemic shunts, renal veins, and the inferior vena cava. Magnetic resonance imaging (MRI) is an alternative to CT in patients with impaired renal function. However, the definition is lower than that of CT, especially in patients with tense ascites [24]. Systematic Doppler US may be recommended every 3 months during waiting time, whenever possible.

In patients with PVT, three approaches can be considered: systemic anticoagulation, transjugular intrahepatic portosystemic shunt (TIPS), and endovascular procedures with fibrinolysis.

Anticoagulation

Whereas the usefulness of anticoagulation in acute PVT without underlying liver disease has been clearly documented [25], only few studies have been conducted in patients with cirrhosis (Table 2). In theory, anticoagulation in cirrhosis is justified by the preserved balance between pro and anticoagulant factors, even when coagulation factors are decreased. Table 2 shows that most series of cirrhotic patients treated by anticoagulation only had partial thrombosis with persistent, although reduced, portal flow. Various protocols have been used including low molecular weight heparin and vitamin K antagonists (VKA). As shown in Table 2, complete recanalization may be achieved in 40–75% of patients while less than 10% experience an extension of the thrombus [4,26,27]. The rate of recanalization is significantly higher in patients receiving anticoagulation than in control patients who do not [4]. In those with complete thrombosis, recanalization seems uncommon but anticoagulation may prevent the extension of the thrombus [28]. Interestingly, anticoagulation does not have a significant impact on blood loss and duration of transplant surgery [4].

There is no consensus on which anticoagulation is best suited in this context. Low molecular weight heparin (LMWH) can be used until transplantation. While LMWH may be safe and as effective as VKA, it is less practical for the patients, with the need for subcutaneous injections. However, one advantage of LMWH is that it does not interfere with the MELD score.

Another option is to start VKA with a target INR of 2–3 [4]. On the one hand, VKA can be given orally and anticoagulation can be reversed rapidly at the time of transplantation by the administration of fresh frozen plasma. On the other hand, monitoring may be difficult in patients with a baseline increase in INR [29]. In a patient with a baseline INR over 2 for instance, it may be difficult to determine if a given dose of VKA ensures adequate anticoagulation. It may also be difficult to determine the optimal INR target for dose adjustment.

Thrombin inhibitors and inhibitors of activated factor X such as dabigatran and rivaroxaban could be an attractive option [30]. These newer agents offer the advantage of oral administration, the absence of laboratory monitoring, and a mechanism of action which is independent of antithrombin [29]. However, no data are available yet in cirrhotic patients who could be at risk of excessive anticoagulation.

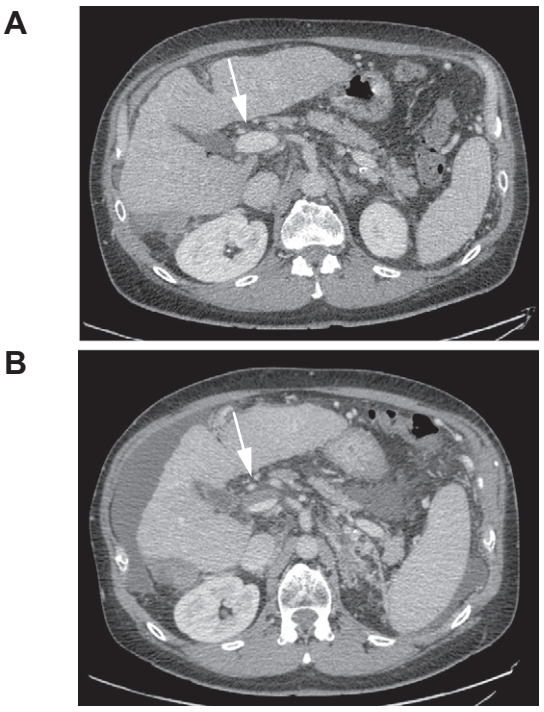

Fig. 1. Helical computed tomography showing patent portal vein (A, white arrow) in a candidate for liver transplantation with alcohol-related cirrhosis at evaluation. Six months later, follow up computed tomography in the same patient shows the occurrence of *de novo* portal vein thrombosis. The thrombus is partial and involves the trunk of the portal vein (B, white arrow).

Even though there is no evidence that anticoagulation increases the risk of variceal bleeding [4,26], it is recommended to check for varices, initiate and/or optimize beta blockers or perform elastic band ligation before starting anticoagulation.

It has been proposed recently that systematic anticoagulant therapy could help prevent PVT in advanced cirrhosis. Preliminary data suggest that enoxaparin for prolonged periods (12 months) could decrease significantly the incidence of *de novo* PVT compared to a placebo, without relevant side effects [31]. These results have to be validated.

Transjugular intrahepatic portosystemic shunt

The objective of TIPS is to recanalize the portal vein and, subsequently, prevent rethrombosis by restoring portal flow through a low resistance shunt. It clearly appears that the feasibility of TIPS varies according to the extent of thrombosis. Technical failure may be related to the absence of visibility of intrahepatic branches of the portal vein, transformation of the portal vein into a fibrous cord and extension of the thrombus to the superior mesenteric vein. However, TIPS may be feasible in some patients with cavernoma [32–35]. In the largest series, feasibility ranged from 70% to 100% (Table 3) [32,33,36]. Applicability could be lower and prospective studies giving the proportion of patients in whom TIPS was not considered due to PVT are needed. Ideally, TIPS insertion and recanalization might be associated with disrupture of the thrombus and mechanical thrombectomy. However, there are only few data on the comparison between feasibility and thrombectomy [36,37]. Even if TIPS insertion is most often associated

Table 2. Efficacy and safety of anticoagulation for portal vein thrombosis in cirrhotic patients.

Author, [Ref.]	Year	Patients	Partial/complete thrombus	Treatment	Complete recanalization (%)	Extension	Treatment-related events
Francoz *et al.*, [4]	2005	19	18/1	Nadroparin or VKA*	42	5%	0
Senzolo *et al.*, [27]	2009	26	-	LMW heparin**	50	-	2†
Amitrano *et al.*, [26]	2010	28	23/5	Enoxaparin	75	7%	0

*VKA, vitamin K antagonist.
**LMW, low molecular weight.
†One episode of heparin-induced thrombocytopenia and one episode of non-variceal bleeding.

Table 3. Feasibility, efficacy, and safety of TIPS in cirrhotic patients with portal vein thrombosis.

Author, [Ref.]	Year	Patients	Complete thrombosis (%)	Feasibility (%)	Encephalopathy (%)	TIPS dysfunction (%)	Long term anticoagulation (%)	Transplantation (%)
Bauer *et al.*, [79]	2006	9	44	100	-	22	11	22
Senzolo *et al.*, [36]	2006	28	82	73	4	26	53	11
Han *et al.*, [32]	2011	57	38	75	25	20	100	-
Luca *et al.*, [37]	2011	70	-	100	27	38	0	21

with thrombectomy, residual thrombosis of the superior mesenteric vein is possible. There is no evidence to recommend either TIPS or anticoagulation as the first line option when both options are available. TIPS should only be considered in experienced centers.

In the perspective of transplantation, the crucial point is that TIPS should not be inserted distally into the portal vein trunk and superior mesenteric vein as it would compromise transplant procedure [38].

In the long term, the rate of dysfunction and/or rethrombosis ranges from 21% to 38% with the need for revision in some patients [32,33,36,37]. About 20–30% develop encephalopathy. Independent of PVT, the rate of dysfunction is significantly lower with covered stents compared to bare stents [39]. However, there is no evidence that covered stents are superior in candidates for transplantation who stay on the waiting list for a relatively limited period of time.

The main limitation of TIPS in this context is that most candidates for transplantation have advanced cirrhosis with a high MELD score. TIPS is generally contraindicated in patients with a high MELD score due to further deterioration in liver function and a high mortality risk. A threshold MELD score value of 18 has been proposed as the upper limit for considering TIPS [40]. Previous episodes of spontaneous encephalopathy also represent a contraindication. Whether patients with a patent TIPS should be placed on long term anticoagulation has been a matter of debate. Several studies have shown that long term patency can be achieved without anticoagulation [32,33,37]. Therefore, except in patients with documented prothrombotic state, systematic anticoagulation should not be recommended.

Overall, anticoagulation and TIPS are two possible options without evidence for superiority of one against the other. The pros and cons of each option are summarized in Table 4.

Endovascular procedures and fibrinolysis

The results of systemic or *in situ* thrombolysis in non-cirrhotic patients with acute PVT have been dismal with a low rate of recanalization and a high incidence of major bleeding [14,41]. Experience in cirrhotic patients with PVT is very limited [42]. A first concern is that it is relatively uncommon to identify recent PVT in cirrhotic patients. A second concern is that transhepatic approach may be more difficult in patients with portal hypertension. There is no data to support this option.

Impact of portal vein thrombosis on organ allocation: is priority justified?

Because the increasing demand in liver transplantation markedly exceeds organ supply, a major concern in the transplant community has been to optimize equity in allograft allocation. Most Western countries have adopted a "sickest first" allocation policy and the MELD score represents the reference tool to determine priority [43,44]. Unfortunately, the MELD score is not a universal prognostic score in cirrhosis. It is inaccurate at predicting outcome in a number of conditions such as refractory ascites and hepatopulmonary syndrome. Such conditions are generally considered MELD exceptions [45]. Whether PVT is an independent risk factor or is a surrogate marker of severity in cirrhosis is still debated [3]. Several studies have shown that PVT could increase post-transplant mortality and morbidity [3,10,46]. By contrast, for a given MELD score, evidence that patients with PVT are at higher risk of waiting list mortality compared to patients without thrombosis is lacking. A recent study based on the Scientific Registry of Transplant Recipients data in the United States has shown that PVT was not an independent predictor of waiting list mortal-

Table 4. The pros and cons of anticoagulation and TIPS in the treatment of portal vein thrombosis in cirrhotic patients awaiting transplantation.

	Anticoagulation	TIPS
Pro	Non-invasive and safe option Documented efficacy in partial thrombosis Anticoagulation is easy to reverse at the time of transplant procedure	Feasibility in 70-80% of patients Recanalization possible in patients with complete portal vein thrombosis Low rate of dysfunction
Con	VKA monitoring and dose adjustment difficult in patients with a baseline increase in INR Potential risk of bleeding Low rate of recanalization in patients with complete thrombosis	TIPS may compromise transplantation in case of misplacement TIPS contraindicated in patients with high MELD score Risk of encephalopathy

Table 5. Surgical options in patients with splanchnic vein thrombosis according to the extent of thrombosis.

Extent of thrombosis at transplantation	Surgical options	Anatomical	Reverses portal hypertension
Partial portal vein thrombosis	Thrombectomy and end-to-end portal anastomosis	yes	yes
Complete portal vein thrombosis	Thrombectomy and end-to-end portal anastomosis	yes	yes
	Jump graft between the SMV* and donor's portal vein	no	yes
Complete thrombosis involving the SMV	Renoportal anastomosis (end-to-end anastomosis between the left portal vein and donor's portal vein ± vascular graft)	no	no**
	Cavoportal hemitransposition ± IVC† calibration	no	no
	Combined multivisceral transplantation including the liver small bowel and pancreas	yes	yes‡

*SMV, superior mesenteric vein.
**Except in patients with patent surgical splenorenal shunt.
†IVC, inferior vena cava.
‡Reversion may not always be complete.

ity [47]. However, this study has not classified the extension of thrombosis.

Practically, PVT is not considered a MELD exception and patients with PVT do not receive extra points for organ allocation [45,48,49].

An important concern is that the MELD score which relies on creatinine, bilirubin and INR is inappropriate in patients receiving VKA [44]. VKA artificially increases INR. As an example, in a patient with creatinine, bilirubin and INR values of 100 μmol/L (1.14 mg/dl), 100 μmol/L (5.8 mg/dl), and 1.0, respectively, the MELD score is 14. If INR rises to 2.5 due to the administration of VKA, there is a 71% increase in the MELD score (MELD score of 24). In this situation, the MELD score would overestimate the risk of early mortality and would over prioritize patients receiving VKA.

In order to overcome this difficulty, the MELD score should be calculated before starting VKA. Thereafter, there are two possible ways to update the MELD score. The first way is to use the so called MELD-XI score which only relies on creatinine and bilirubin with the following equation: MELD-XI = 5.11 * Ln(bilirubin [mg/dl]) + 11.76 * Ln(creatinine [mg/dL]) + 9.44 [50]. The MELD-XI is normalized to the same scale as the MELD score. However, it can be argued that the MELD-XI does not take into account baseline coagulation, which is an important prognostic factor. Another way is to use factor V (which is not affected by VKA) instead of INR. Indeed, there is a strong but non-linear correlation between INR and factor V. INR can be estimated from factor V according to the following equation: INR = (factor V [% of normal]/94.9)$^{-0.81}$ [51]. The accuracy of the MELD-XI and that of the change from INR to factor V need further evaluations.

Impact on liver transplant procedure

The technical options for transplantation vary according to the patency of the portal vein and that of other splanchnic veins. When full patency of the portal vein has been achieved, whatever anticoagulation or TIPS have been used pre-transplantation, "conventional" end-to-end portal anastomosis is the first line option. When full patency has not been achieved, the technical option depends upon the extent of PVT (i.e., partial or complete) and the patency of splenic and mesenteric veins. The different surgical options are presented in Table 5.

Patients with partial portal vein thrombosis

In patients who still have partial PVT at the time of transplantation, the objective is to optimize portal blood flow to the graft. Removal of the clot within the portal vein by eversion thrombectomy or thrombendvenectomy (i.e., removal of the clot and the attached intimal layer of the vein) is the reference technique [6,8,9,52,53]. Following complete dissection, the portal vein should be maintained open with tonsil clamps and the clot should be circumferentially freed and removed while the venous wall is everted [9]. The maneuver may be extended to the splenic and/or superior mesenteric vein when needed. Before completing the anastomosis, portal flow is verified by removing the clamps and the portal vein is flushed. Eventually, an end-to-end portal anastomosis is performed as close as possible to the origin of the native portal vein [6]. Interposition of a vascular graft should be avoided whenever possible [8]. If, while the clot has been removed, portal flow remains insufficient, ligation of the collateral circulation

(especially splenorenal shunts) should be performed. However, there is no evidence that collateral circulation should be systematically ligated.

In most series, patients who underwent transplantation with thrombectomy received low molecular weight heparin within the first months following transplantation. Long term administration of anticoagulation was not considered even though, in some series, patients were systematically placed on aspirin [9], an option which is not specific to PVT.

Patients with complete thrombosis limited to the portal vein

Thrombectomy or thrombendvenectomy may be possible even in some patients with complete PVT [6,9] (Fig. 2). According to the technique described above, portal flow should be restored, allowing end-to-end portal anastomosis. However, when the native portal vein corresponds to a fibrotic remnant and/or when the thrombus involves the splenomesenteric confluence, it may be impossible to restore adequate blood flow into the portal vein. In this situation, the distal mesenteric vein can be used as the inflow vessel. Portal flow to the allograft is restored through the interposition of an iliac donor vein as a jump graft between the distal superior mesenteric vein and the donor portal vein [6,53,54]. The extra anatomic jump graft is placed anterior to the pancreas and posterior to the stomach [54]. Again, if the blood flow to the donor's portal vein is not optimal, large portosystemic shunts may be ligated. Endovascular radiological procedures consisting in the identification and embolization of large shunts with coils have been proposed as an alternative to surgical ligation [55]. Eventually, it has been suggested that the donor's portal vein may be successfully implanted onto collateral vessels [52].

Portal vein arterialization consists in improving portal flow by creating an anastomosis between an arterial branch and the donor's portal vein [56]. Arterialization may be performed using the recipient's hepatic artery through a side-to-side anastomosis, an iliac graft between the aorta and the portal vein or an arterial branch of the coeliac axis [56,57]. Only case reports or small series have been published, showing that calibrated arterialization may help restore portal flow without overt portal hypertension. However, aneurysmal dilatation of the portal vein has been reported in the long term [56].

Systematic use of extracorporeal veno-venous bypass in patients with PVT has been advocated in order to prevent the hemodynamic consequences of inferior vena cava and portal vein clamping during the procedure [6]. However, patients who already have portal vein obstruction and who, as a consequence, have developed large and/or multiple collateral vessels are unlikely to present significant hemodynamic changes following clamping of the remnant splanchnic vessels. No data support systematic use of veno-venous bypass.

Patients with diffuse splanchnic vein thrombosis

When complete thrombosis extends to the portal vein, the splenic vein and the superior mesenteric vein distally, no splanchnic vessel can be used as physiological inflow vessels. Patients with extensive thrombosis frequently have complex portosystemic derivations with cavernoma (Fig. 3). Two alternative techniques using systemic veins as the inflow vessels have been proposed: cavoportal hemitransposition and reno-portal anastomosis [58–60].

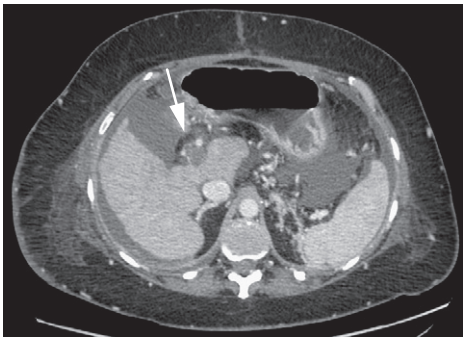

Fig. 2. Helical computed tomography showing complete obstruction of the main trunk of portal vein (white arrow) by a cruoric thrombus in a patient with alcoholic cirrhosis.

In cavoportal hemitransposition, the inflow comes from the inferior vena cava which is anastomosed to the donor's portal vein in an end-to-end, end-to-side or side-to-end fashion [58,59]. The suprarenal vena cava, over the anastomosis, can be calibrated to direct preferentially the blood flow to the portal vein. However, complete obstruction of the inferior vena cava may increase the risk of congestion with impaired renal function and lower limb edema.

In renoportal anastomosis, the portal inflow comes from the left renal vein which is directly anastomosed to the donor's portal vein in and end-to-end fashion [58,61–63] (Fig. 4). Alternatively, the interposition of an iliac vein graft from the donor may be used.

Renoportal anastomosis is best suited in patients who had surgical splenorenal shunt, provided it remains patent [64]. Indeed, the splenorenal shunt, which should not be occluded, results in a decompression of the splanchnic system with a beneficial impact on portal hypertension [59]. In patients without previous splenorenal shunt, the choice between cavoportal hemitransposition and renoportal anastomosis depends upon individual anatomical considerations and technical skills. Importantly, it must be noted that, in contrast to anatomical procedures, these non-anatomical procedures where the portal inflow comes from a systemic vein do not fully reverse portal hypertension (with the exception of patients with a previous surgical splenorenal shunt).

As these non-anatomical options do not reverse portal hypertension, multivisceral transplantation including the liver, small bowel and pancreas has been proposed in diffuse thrombosis and life-threatening upper digestive bleeding [65]. The organs are procured *en bloc* and the blood flow is re-established through the donor's celiac trunk anastomosed to the recipient's infrarenal aorta. In theory, for anatomical reasons, multivisceral transplantation including the liver and the small bowel represents the best option in patients with diffuse splanchnic vein thrombosis as it restores physiological portal blood flow and reverses portal hypertension. However, it is a complex procedure and the high rate of rejection of the small bowel is a limiting factor [66]. In a context of drastic organ shortage, more data are needed on the individual survival benefit of this approach.

Impact of portal vein thrombosis on living donor liver transplantation

Living donor transplantation may be even more difficult than deceased donor transplantation in patients with PVT for several reasons. A partial graft procured from a living donor only has a

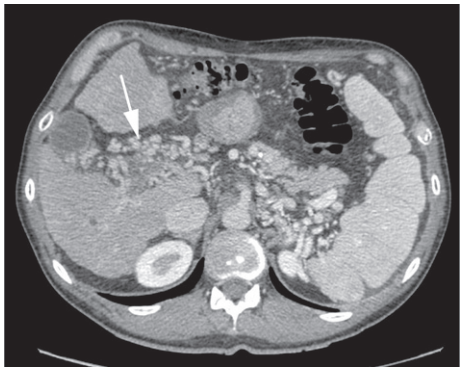

Fig. 3. Helical computed tomography showing organized portal vein thrombosis with cavernoma (white arrow) in a cirrhotic patient at evaluation. The trunk of the portal vein which is no longer visible is surrounded by numerous collateral vessels.

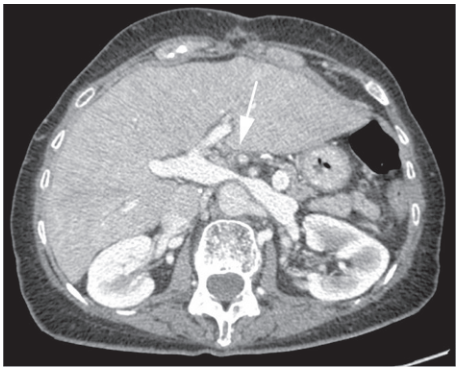

Fig. 4. Helical computed tomography showing patent left renoportal anastomosis (white arrow) 2 years after liver transplantation in a patient with complete obstruction of the portal and mesenteric veins at the time of the procedure.

very short length of portal vein. The recipient's portal vein must be long enough to complete the anastomosis with the graft [67,68]. Finally, procurement of additional vessels for complex reconstruction or jump graft is limited. Indeed, morbidity in the donor should be as low as possible.

Several reports, however, have shown that PVT is not an absolute contraindication for living donor transplantation [67–69]. This is especially important since, as well as in recipients of a deceased donor, some recipients in living donor transplantation may be found with previously undetected thrombosis at the time of the procedure [67,68]. In previous series, most patients had partial thrombosis that could be removed by eversion thrombectomy allowing end-to-end portal anastomosis. When patency could not be achieved and/or the native portal vein was not long enough, an iliac or jugular vein procured in the recipient could be used for reconstruction [68]. Finally, some patients had caval transposition with dismal results [68]. In general, patients with extensive splanchnic vein thrombosis should not be oriented to living donor transplantation due to more technical difficulties and a high mortality rate [70].

Post-transplant outcome

Several studies comparing cirrhotic patients with and without PVT did not find significant differences in terms of post-transplant survival [6–9]. However, the largest series that has been reported so far suggests that, independent of the MELD score, pre-transplant PVT may be associated with a 50% increase in 1-year mortality risk post-transplant [47]. The results of this study also suggest that after the first year, PVT no longer impacts negatively on the outcome [47]. Mortality varies according to the extension of the thrombus and the surgical procedure. In patients with PVT, when end-to-end portal anastomosis can be performed, whatever PVT is partial or complete, the results are similar to those in patients without PVT. One and 5-year survival ranges from 84% to 86% and from 65% to 80%, respectively [5,6,8,9,53]. In contrast, alternative surgical techniques used when end-to-end portal anastomosis is not feasible are associated with a worse prognosis. For instance, early post-operative mortality risk in renoportal anastomosis and cavoportal hemitransposition is of about 25% [58]. One and 5-year survival rate following these techniques may be of only 60% and 38%, respectively [59]. Not only does PVT increase post-transplant mortality, it also increases morbidity. Post-transplant morbidity includes gastrointestinal bleeding due to persistent portal hypertension in about 30% [58,59,62,63], ascites, renal dysfunction [58] and sepsis [8,58,59,62,63]. Prophylaxis against post-transplant variceal bleeding should be applied including beta-blockers and/or endoscopic band ligation. Thrombotic events have also been reported including thrombosis of the anastomosis as well as pulmonary embolism and hepatic artery thrombosis [58,59]. Patients with underlying prothrombotic states are likely to be at increased risk for these events.

Transplant survival benefit, namely, the net difference between survival with medical management alone and survival with transplantation emerged as an attractive tool to identify patients who would justify transplantation in the context of organ shortage and those who do not [71]. In patients with a low MELD score, transplantation may be even more hazardous than remaining on the waiting list due to the intrinsic mortality and morbidity of the procedure. A recent study has shown that the threshold corresponding to transplant benefit may be slightly higher in patients with PVT than in patients without thrombosis (MELD score of 13 *vs.* 11, respectively) [47]. The difference is likely to be due to higher morbidity and mortality in those with thrombosis. However, it must be noted that there is no agreement on which threshold MELD score value clearly identifies patients who derive a survival benefit from transplantation in general [47,71]. In addition, this low threshold value (MELD score of 13) is not even compatible with listing for transplantation in many countries where the scarcity of organs leads to transplant the sickest patients [47]. Practically, such a low value may be unrealistic.

Post-transplant rethrombosis, anticoagulation, and screening

Rethrombosis is a potential complication in patients with pre-transplant PVT. Early rethrombosis generally results in graft loss with the need for emergency re-transplantation (if possible) [72]. There are few data on the impact of delayed PVT post-transplantation. Experience shows that delayed PVT does not necessarily lead to graft failure. The main consequences are related to portal hypertension.

In theory, long term anticoagulation could help reduce the risk of rethrombosis. For instance, patients with myeloproliferative disorders and Budd–Chiari syndrome as the indication for transplan-

tation are generally given long term anticoagulation in order to prevent recurrence [73,74]. However, existing data suggest that in contrast to the hepatic vein thrombosis, pre-transplant PVT does not justify long term anticoagulation. Firstly, in the largest series of cirrhotic patients with PVT undergoing transplantation, long term VKA were not considered [5,6,8,9]. Secondly, even in the absence of long term VKA, the rate of rethrombosis in patients who had end-to-end portal anastomosis was very low (less than 5%) [5,6,8,9]. Finally, as discussed above, PVT in cirrhotic patients is more likely to be due to hemodynamic changes (decreased portal flow) than to coagulation disorders. In addition, inherited coagulation disorders, if present, are likely to be cured by liver transplantation as the genome of the allograft turns to be that of the donor. If adequate portal flow to the allograft is restored and the anastomosis is anatomical, the risk of rethrombosis seems to be low.

In patients with extensive thrombosis and non-anatomical procedure (Table 5) such as caval transposition, the rate of rethrombosis is higher [58,59]. Whether the high rate of rethrombosis is related to an underlying prothrombotic state or to complex anastomoses is unclear. Early post-operative anticoagulation should be recommended. The place of long term anticoagulation in this subgroup still has to be determined.

Antiplatelet prophylaxis aiming at preventing hepatic artery thrombosis and other cardiovascular complications is frequently used after liver transplantation [75]. The effect of low dose aspirin on the occurrence of venous thrombosis is contrasting. Some studies have shown that a short course of aspirin may reduce significantly the occurrence of venous thromboembolism in high risk patients [76,77]. However, evidence that long term aspirin lowers venous thromboembolism in low risk patients is lacking [78]. There are no data in liver transplant recipients with a history of PVT.

Overall, in patients with anatomical portal anastomosis and adequate portal flow, a short course of heparin or fractionated heparin may be recommended within the first post-operative days to minimize the risk of early rethrombosis. However, no data support the use of long term anticoagulation. Patients with documented prothrombotic state should receive long term anticoagulation provided the prothrombotic state has not been reversed by transplantation. Lifelong VKA remains the first option. In patients with renoportal anastomosis or caval transposition, the high rate of rethrombosis argues for prolonged anticoagulation with VKA, even in the absence of prothrombotic state.

Conclusions

Decreased coagulation factors and low platelet count are not protective against PVT in cirrhosis. Portal hypertension and low portal flow are the main factors leading to PVT. PVT is rarely a definitive contraindication for transplantation. However, it is a source of technical difficulties with increased morbidity and mortality. Too many patients are still found with previously unrecognized thrombosis at the time of transplantation emphasizing the need for more accurate screening. The main objective in the management of patients with PVT is to allow conventional end-to-end portal anastomosis with a physiological portal flow to the allograft. Anticoagulation and TIPS are the main options to achieve these goals. When both are feasible, there is no evidence that one option is definitely superior to the other. However, even when technically feasible, TIPS may be contraindicated in patients with severe impairment in liver function,

Key Points

- Portal vein thrombosis, either partial or complete, is found in between 5 to 25% of cirrhotic patients undergoing liver transplantation. During the transplant procedure, a substantial proportion of cirrhotic patients are found to have previously unrecognized portal vein thrombosis despite detailed imaging at evaluation
- In cirrhotic patients, the increase in intrahepatic vascular resistance and decreased portal blood flow is likely to be a predisposing factor for portal vein thrombosis. However, whether reduced portal blood flow is the major cause or is a cofactor needs to be further addressed
- The objective in the management of portal vein thrombosis pre-transplantation is to preserve or restore portal flow so that anatomical end-to-end portal anastomomosis can be performed
- Anticoagulation (low molecular weight heparin [LMWH] or vitamin K antagonists [VKA]) and TIPS are two options to achieve portal vein patency and/or prevent the extension of the thrombus during waiting time. VKA allow complete recanalization in about 40 to 75% of patients with partial thrombosis without increasing the risk of bleeding during waiting time. LMWH is an alternative with comparable safety and efficacy profile. Anticoagulation seems to be less effective in patients with complete thrombosis. However, more data is needed
- The MELD score is not valid in patients receiving VKA as these agents artificially increase INR.The MELD score would overestimate mortality risk and would over-prioritize in patients receiving VKA
- TIPS is feasible in 75% to 100% of patients with portal vein thrombosis. However, in patients with advanced cirrhosis (MELD score over 18), TIPS may have an increased risk of further deteriorating liver function and of increasing mortality
- In the perspective of transplantation, TIPS should not be inserted distally into the portal vein, close to the terminal portion of the superior mesenteric vein or into the inferior vena cava. Misplacement may preclude portal anastomosis
- In patients with diffuse thrombosis, alternative non-anatomical techniques include renoportal anastomosis or caval hemitransposition. These techniques may not reverse portal hypertension
- There is no evidence that portal vein thrombosis *per se* increases waiting list mortality, independent of the MELD score. However, portal vein thrombosis is associated with increased post-transplant mortality and morbidity, especially when thrombosis is complete and extensive
- Anticoagulation in the early post-transplant course is recommended to prevent rethrombosis. However, long term anticoagulation is not justified in patients with pre-transplant portal vein thrombosis provided anatomical end-to-end portal anastomosis can be performed and there is no underlying persistent prothrombotic state

which is common in candidates for transplantation. Anticoagulation may consist in LMWH or VKA. The management of VKA in patients with a marked baseline decrease in coagulation factors may be difficult. Novel agents that do not require laboratory monitoring may be attractive in this context. Efforts should be made to better identify patients with cirrhosis at high risk for developing portal vein thrombosis, as prophylactic measures may be justified.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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